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EFFECT OF METRONIDAZOLE ('FLAGYL') UPON NON-GONOCOCCAL URETHRITIS IN THE MALE*

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Metronidazole (8823 RP; "Flagyl") is a nitroinidazole derivative which has been shewn to be highly active against *T. vaginalis*, not only in the laboratory (Cosar and Julou, 1959) but also *in vivo* against human trichomoniasis in the female (Durel, Roiron, Siboulet, and Borel, 1959, 1960; Durel, Couture, Collart, and Girot, 1960; Nicol, Barrow, and Redmond, 1960; Rodin, King, Nicol, and Barrow, 1960; Watt and Jennison, 1960; Willcox, 1960). At last, therefore, an effective systemic treatment for trichomoniasis is available and usually local therapy is no longer necessary.

That *T. vaginalis* is found in males with non-gonococcal urethritis (NGU) is well known. Sylvestre, Belanger, and Gallai (1960) tabulated the incidence found by numerous workers: the highest (in 68 per cent. of NGU cases) was reported in the series of Coutts and Silva-Inzunza (1957) in Chile, and an incidence of 41 per cent. was reported by Feo and Fetter (1958) in Philadelphia. Generally lower figures have been reported from Great Britain: *e.g.* 15·3 per cent. by Whittington (1951) and 5·8 per cent. by Lanceley (1953). The wide variation of incidence prompts the suggestion that a significant proportion of NGU cases may be associated with *T. vaginalis* but that existing diagnostic methods may be inadequate for the detection of this organism.

Certainly, in those cases of NGU in which *T. vaginalis* is found, the parasite can be removed by Metronidazole given orally. Durel, Roiron, and others (1960) had success in all of thirteen male cases (although there was some persistence of the discharge in three cases and one relapse which was cured by re-treatment). Sylvestre and others (1960) claimed that *T. vaginalis* disappeared from all of 27 cases of trichomonal urethritis. Nicol and others (1960) likewise had no immediate or late failures in eleven cases, although discharge without *T. vaginalis* persisted in two cases. Rodin and others (1960) treated seventeen cases of *T. vaginalis* infestation associated with urethritis and obtained a good response in thirteen cases; local complications were present in the remaining four cases.

There is so far little information concerning the effects of Metronidazole in cases of NGU in which *T. vaginalis* is not found by direct smear or culture examination: moreover the available data are conflicting. Thus Durel, Roiron, and others (1960) reported that their results were "practically negative" in fourteen cases, whereas Sylvestre and others (1960) reported success in all of five cases in which *T. vaginalis* was not found (although the female consorts of these patients were known to have harboured the parasite). It was felt worthwhile, therefore, to treat with Metronidazole a larger series of patients with NGU in whom *T. vaginalis* had been excluded by wet smear and/or culture examinations of material from the urethra or prostate before treatment.

Material

70 males with NGU were treated with Metronidazole ("Flagyl"). Their average age was 28·2 years (range 18–58). Nineteen were Negroes (14 from the West Indies, four from West Africa, and one from Uganda). Of the remaining 51, 27 were from the United Kingdom, five from Eire, three from Cyprus, two from India, two from Hong Kong, and one each from Australia, Belgium,

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Ceylon, Israel, Italy, Jordan, Malta, Pakistan, Persia, Poland, Portugal, and Sweden, respectively. Nineteen were married (one divorced) and 51 were single.

34 (11 of whom were Negro) had had no previous venereal incident. The remaining 36 had had between them 37 attacks of gonorrhoea, 34 of NGU, three of venereophobia, one of syphilis and one of genital oedema; 38 of these 76 incidents had occurred in the 21 Negroes.

The discharge had been present before treatment for 1 to 3 days in 35 cases, 4 to 7 days in sixteen, 8 to 14 in fourteen, and more than 14 days in five. Dysuria was reported by 27 patients, 32 had no dysuria, and eleven gave no information. The disease had apparently been caught from a stranger in 31 cases, from a friend in 33, from the wife in five, and from an unknown source in one. The apparent incubation period was 1 to 3 days in seventeen cases, 4 to 7 in fourteen, 8 to 14 in fifteen, 15 to 21 in five, and over one month in eight; in eleven cases it was not possible to assess the incubation period.

Methods

Gonococci were excluded in the urethral smear in all cases before treatment. Wet smears and cultures were used to exclude trichomonads in the urethral or prostatic secretion in 54 cases, with negative results in all. The Wassermann and V.D.R.L. (or Kahn) reactions before treatment were both negative in 67 cases, the Wassermann reaction was negative and the other test positive in two cases, and both were positive in one case. All non-negative results were in West Indian patients, and were doubtless due to past yaws in some instances.

All patients were treated with one 200-mg. tablet of "Flagyl" three times daily for one week. No side-effects were reported. The patients were instructed to attend 1, 2, and 3 weeks after treatment, and thereafter at longer intervals until 3 months had elapsed. Not all the patients attended at the times requested.

Follow-up and Results

The follow-up and results are shewn in Table I.

TABLE I

NON-GONOCOCCAL URETHRITIS TREATED WITH METRONIDAZOLE

Length of Follow-up (days)	Cases Followed	Result		
		No. Satisfactory	No. with Gonococcal Infection	No. of Failures
0	70	—	—	—
1– 7	58	8	1	16
8–14	33	6	4	7
15–21	16	1	1	1
22–28	13	2	—	2
30–60	9	4	—	1
61–90	4	1	—	1
More than 90	2	1	1	—
Total ..	58	23	7	28

Of seventy patients treated, 58 were followed, and the status was satisfactory at the last visit in 23 of them. Seven patients were found subsequently to have a gonococcal infection and there were 28 failures (48·3 per cent. of those followed) within 3 post-treatment months.

Comparison with Other Methods.—The results obtained with Metronidazole were similar to those noted with aminitrozole (Table II, opposite).

Metronidazole must therefore be considered ineffective in cases of NGU in which trichomonads are not found.

Summary

(1) Previous reports of the considerable efficacy of Metronidazole in the treatment of trichomoniasis are reviewed.

(2) Metronidazole was given to seventy male patients with non-gonococcal urethritis in whom trichomonads were not found. Re-treatment with other drugs proved necessary in 28 (48·3 per cent.) of 58 patients followed for up to 3 months.

(3) Metronidazole is thus not effective in the common run of cases of non-gonococcal urethritis. The results obtained are compared with previous experience of sixteen other antibiotic and chemotherapeutic substances (Willcox, 1960).

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TABLE II

RESULTS OF TREATMENT OF NON-GONOCOCCAL URETHRITIS WITH DIFFERENT SUBSTANCES

Drug	Usual Dosage (g.)	Cases Treated	Cases Followed	Results	
				No. of Failures	Percentage Failures of Those Followed
Tetracycline and Oleandomycin	6	106	82	12	14·6
Oxytetracycline	5– 6	85	82	13	15·9
Tetracycline hydrochloride	6	124	108	20	18·5
Chlortetracycline	5– 6	115	108	20	18·5
Spiramycin	10–20	134	123	25	20·5
Streptomycin plus Sulphonamide	1+12	100	79	20	25·3
Erythromycin	6	101	85	23	27·1
Triacetyloleandomycin	6	100	85	19	27·1
Tetracycline phosphate*	4	150	130	36	27·7
Sulphonamides	12–28	155	141	54	38·3
Streptomycin†	1– 4	164	141	65	39·6
Penicillin	1–3·6 mega units	70	65	26	40·0
Chloramphenicol	5– 6	39	37	15	40·5
Metronidazole	4·2	70	58	28	48·3
Aminitrozole	1·8–2·1	49	45	22	48·9
Novobiocin	6–12	40	36	20	55·6
Placebo	—	29	22	15	68·2
Total		1,631	1,427	433	26·5

* With and without 4 mg. methylprednisolone. † With and without phenylbutazone.

Résultats du traitement de l'urétrite non-gonococcique avec le Metronidazole (Flagyl).

RÉSUMÉ

(1) L'auteur passe en revue les nombreux rapports récents sur l'efficacité remarquable du Metronidazole dans le traitement de la trichomoniase.

(2) 70 hommes atteints d'urétrite non-gonococcique, chez qui on ne trouva pas de trichomonades, ont reçu du Metronidazole. Chez 28 sur 58 (48%), dont on pouvait suivre le progrès, il était nécessaire d'employer un autre médicament pour achever une guérison.

(3) Le Metronidazole n'est pas donc efficace dans la plupart des cas d'urétrite non-gonococcique. Ces résultats sont mis en comparaison avec ceux obtenus auparavant avec 16 médicaments antibiotiques et chimiothérapeutiques.